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**COMMENTS OF
THE CLOROX COMPANY**

**For the Proposed Reclassification of
Respirable Crystalline Silica**

**National Toxicology Program (NTP) Board of Scientific
Counselors' Meeting**

**Review of Nomination for Listing in or Delisting
from the 9th Report on Carcinogens**

December 2-3, 1998

SUMMARY

The Federal Register of October 26, 1998 (Vol. 63, Number 206, pages 57132-57133) has given notice that a National Toxicology Program (NTP) Board of Scientific Counselors' Meeting has been scheduled to review nominations for listing or delisting. The listing of respirable silica, crystalline (CAS Number 7631-86-9)¹, among other chemicals, has been proposed to be changed from 'reasonably anticipated to be a human carcinogen' to 'known to be a human carcinogen'.

In these materials, The Clorox Company presents conclusive data to show that forms of respirable crystalline silica, specifically, unfractured occluded quartz or low crystallinity polycrystalline chert, are *not* 'known to be a human carcinogen' and further that they do not meet criteria to continue to be listed as "reasonably anticipated to be a human carcinogen" because they do not meet NTP's criteria for listing chemicals in the Report on Carcinogens. We will show that:

- Unfractured, occluded quartz or low crystallinity polycrystalline quartz, do not meet NTP's criteria for listing chemicals in the Report on Carcinogens. This conclusion is

¹ Although the Federal Register notice describes the chemical under consideration for reclassification as CAS Number 7631-86-9, we believe this designation may possibly be a typographical or inadvertent error, and we request clarification. The current NTP classification for respirable crystalline silica in the NTP Annual Report on Carcinogens applies to silica forms designated as 14808-60-7, 14464-46-1 and 15468-32-3. CAS Number 7631-86-9 is the designated CAS Number for amorphous silica which, to our knowledge, has not been classified by NTP. In addition, the International Agency for Research on Cancer ("IARC") classifies this form of silica as a Category 3 chemical under the IARC classification scheme (see IARC Monographs on the Evaluation of Carcinogenic Risk To Humans, Volume 68, Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils ("IARC 1997 Monograph"), 1997, p.211). The chemicals that properly should be considered for NTP reclassification are limited to CAS Nos. 14808-60-7, 14464-46-1 and 15468-32-2.

supported by or is consistent with IARC's 1997 Monograph and the relevant underlying human and animal test data.

- IARC's classification of certain forms of silica as Category I does not apply to any nonoccupational exposures or to all forms of respirable silica. Although IARC previously classified all forms of respirable crystalline silica, it no longer does so.
- The toxicological mechanisms of action for fractured crystalline silica leading to carcinogenesis which were elucidated in animal studies are not predictive of known biological responses in humans exposed to unfractured occluded quartz or low crystallinity polycrystalline quartz.

Silica Surface Chemistry

Fractured, Unoccluded vs. Unfractured, Occluded

The silicate minerals are the largest group of minerals with a three-dimensional network of silica tetrahedra. Because of its unique geometry, silica is found as one of at least eight polymorphs. Numerous researchers have demonstrated major differences in the biological activities of the polymorphs. The morphological differences between these polymorphs are key to understanding their chemical differences which cause different biological and carcinogenic responses. The interactions between minerals, in particular silica, with living matter depends on its morphology and the reactivity of its surfaces.

Crystalline silica is generally composed of a regular arrangement of silicon-oxygen tetrahedra which share their corners with the succeeding tetrahedra. The unique three-dimensional structural feature of quartz is that it is composed of a helical arrangement of the tetrahedra along the c-axis of the helix and each helix has a repeat distance of three tetrahedra units (IARC 1997 Monograph, p. 45). When quartz crystals are fractured, the helical chain of the Si-O tetrahedrons are broken leaving Si or O radicals present at the surface of the fractured crystal (Vallyanthan *et al.*, 1988; Fubini *et al.*, 1995; IARC 1997 Monograph, p. 49). These chemically and biologically reactive radicals interact with other chemicals and over time are eliminated; they are only present on 'freshly fractured' quartz surfaces. Unfractured surfaces consist of stable nonreactive molecules. For freshly fractured quartz, the Si and O radicals on the fractured particle surface can then react with biological molecules (Vallyanthan *et al.*, 1988; Shoemaker *et al.*, 1995; Vallyanthan *et al.*, 1995). This biological response forms the basis of the mechanism of carcinogenicity as presented by IARC in their 1997 monograph.

Occluding the quartz surface (e.g., by coating it with another material such as silicates, metals, coal or clay) provides both a physical and chemical barrier preventing the interaction of these reactive Si and O radicals with biological molecules. Thus, only fractured unoccluded quartz has reactive Si and O radicals which are the basis for the proposed mechanism of carcinogenic response as discussed later. The morphological differences between freshly fractured and unfractured quartz relate both to structural and chemical differences which are key to understanding the biological and carcinogenic response that each can elicit.

The use of freshly ground silicas have demonstrated a high degree of toxicity which can be attributed to the new surface chemistry, such as reactive oxygen radicals. Grinding or fracturing results in reactive species which may ultimately lead to active oxygen species on the surface. Freshly fractured silica in *in vitro* studies have lead to an increased incidence of cell membrane damage, membrane lipid peroxidative mechanisms and alveolar macrophage activation. In fact, acute damage has been shown to occur in workers in the drilling, mining and sandblasting occupations and who have been exposed to freshly ground respirable silica. Those forms of silica which are aged or occluded, and do not possess any surface radical chemistry do not produce any pathogenic processes as seen in freshly fractured quartz. (see IARC 1997 Monograph, p. 191).

Occupational Exposures

The occupational exposures supporting the 1997 IARC determination were associated with ore mining; quarries and granite production; ceramics, pottery or refractory bricks manufacturing; and calcining diatomaceous earth. Because of the severe processing or heating of materials common to these industries or natural processes, the crystalline silica content of materials results in a freshly fractured surface, *i.e.*, fractured quartz or the production of more carcinogenic forms of crystalline silica, such as cristobalite and tridymite (IARC 1997 Monograph, pp. 65-77). These industries produce biologically active species of crystalline silica.

Although the portion of the IARC 1997 Monograph applicable to silica did not evaluate industries associated with exposure to unfractured occluded quartz and/or low crystallinity polycrystalline quartz, other parts of the monograph did. In those instances, IARC did not find sufficient evidence of carcinogenicity in humans. The single study in the silica portion of the IARC 1997 Monograph referring to unfractured occluded quartz and/or low crystallinity polycrystalline quartz, was a study of workers at several tungsten or copper/tin mines, potteries and a single clay mine (the latter being the only one to produce exposures to unfractured occluded quartz and/or low crystallinity polycrystalline quartz) (Chen, 1992; IARC 1997 Monograph, p. 97). While that study found a decrease in expected lung cancers, we understand from a co-author of the study that the authors did not evaluate the clay mine data in reaching their conclusions.

The most relevant occupational exposure studies for evaluating the potential carcinogenicity of aged and occluded crystalline silica are coal miner epidemiology studies because the crystalline silica present in coal dust is more likely to be primarily occluded in the coal dust than particles released by other mining activities. Bituminous coal miner studies in particular are the most relevant due to the concentration of silica present in bituminous coal relative to anthracite coal and the lower concentrations of free fractured quartz dust generated from moving, blasting or excavating sedimentary rock structures (Kuempel *et al.*, 1995; NIOSH, 1995). Regardless of the type of coal mining evaluated, there is *no* evidence of an increased risk of lung cancer in coal miners attributable to unfractured occluded quartz and/or low crystallinity polycrystalline quartz (see IARC 1997 Monograph, pp. 337-393; Kennaway & Kennaway, 1947; James, 1955; Stocks, 1962; Enterline, 1972; Goldman, 1965; Costello *et al.*, 1974;

Rockette, 1977; Cochrane *et al.*, 1979; Ames *et al.*, 1983; Miller & Jacobsen, 1985; Meijers *et al.*, 1991; Swaen *et al.*, 1995; Starzynski *et al.*, 1996).

Environmental Studies. Additional human studies reveal no association between exposure to unfractured occluded quartz and/or low crystallinity polycrystalline quartz and cancer. Two studies of environmental, chronic exposure to high levels of aged crystalline silica present in desert dust (60 percent of desert sand dust is crystalline silica) did not result in an increased incidence of cancer in desert inhabitants (Pollicar & Collet, 1952; Bar-Ziv & Goldberg, 1974). Although IARC cited the study by Bar-Ziv and Goldberg in its 1987 Monograph, it did so only to identify circumstances of exposure and did not review the study's conclusions concerning carcinogenicity (IARC 1987 Monograph, p. 72).

The data from these studies of desert inhabitants indicate that environmental exposure to unfractured occluded quartz and/or low crystallinity polycrystalline quartz does not elicit a carcinogenic response in humans. As discussed above, IARC concluded in 1997 that the only evidence of carcinogenicity in humans was from exposure to respirable crystalline silica from specific occupational sources. The occupational studies were of silica forms other than unfractured occluded quartz and/or low crystallinity polycrystalline quartz. All studies of exposure to silica, regardless of form, from non-occupational sources were negative (Pollicard & Collet, 1952; Bar-Ziv & Goldberg, 1974).

In summary, there is no human evidence of a causal relationship between cancer and unfractured occluded quartz and/or low crystallinity polycrystalline quartz from *any* source. There is also no human evidence of a relationship between crystalline silica, regardless of form, from non-occupational sources and cancer.

NTP's criteria for listing a chemical as 'known to be a human carcinogen' requires sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the chemical and human cancer. The criteria set forth by NTP is not met for unfractured occluded quartz and/or low crystallinity polycrystalline quartz for the reasons discussed above.

Rodent Mechanisms of Inhalation Pathology are not Relevant to Human Exposures

The basic assumption concerning a valid and plausible hazard characterization is dependent on whether or not the pathological effects observed in the animal species tested would also occur in humans and the basic mechanistic considerations of the effect seen in the animals are also applicable to humans. Since various rodent species are used to understand the health concerns associated with human inhalation exposures, it is especially important to ascertain the relevance of these rodents mechanisms to human exposures. With respect to rats, it has been demonstrated repeatedly that when exposed to solid relatively inert respirable particles via inhalation or intratracheal administration, this rodent's pulmonary responses are not predictive of human responses. In fact, rats, but not mice, hamster, or guinea pigs, readily develop lung tumors when exposed

chronically by inhalation to relatively inert respirable solid particles. Relatively inert materials, such as talc and titanium dioxide, have produced lung cancer in rats, although these same materials have not caused lung cancer in other species (Driscoll, 1995). Rats have an exaggerated response to particles when lung clearance mechanisms are overloaded (Mauderly and McCunney, 1996; McClellan, 1996, 1997).

Particle Lung Overload

The most prominent effect of particle lung overload in chronic rat inhalation is a significant prolongation of alveolar macrophage-mediated particle clearance. In rats, adverse effects and potential pathogenic events include activation of alveolar macrophages and uptake by macrophages and polymorphonuclear lymphocytes (PMN) in the activation of these inflammatory cells leads to release of numerous mediators, proteases, oxygen radicals, nitrogen radicals, growth factors, cytokines, such as TNF- α , IL-1 and IL-6, and chemokines. Subsequent effects include epithelial damage, increased epithelial cell proliferation and recruitment of inflammatory cells. Increased epithelial cell proliferation may increase the number and survival of transformed cells and therefore increase chances for development of lung tumors.

The rat responds to chronic high particle exposures with pulmonary inflammation, fibrosis and lung tumors. In contrast, mice and hamsters fibrotic reactions have not been observed and no lung tumors can be induced in long-term particle inhalation studies. In humans, inflammatory, as well as fibrotic reactions, have been observed but no increased incidence of lung tumors. The IARC 1997 Monograph states that in rats a significantly greater neutrophil-mediated inflammatory response occurs in silica-induced lung tumors compared to humans (5% in human silicotics vs. 30-50% in rats). This marked quartz-induced inflammatory response may explain rat sensitivity to quartz- and particle- induced lung tumors. The relevance of the mechanisms at work for rat lung tumor formation from quartz exposure is further weakened by the fact that other laboratory animals (*i.e.*, hamster and mouse) do not develop lung tumors after exposure to poorly soluble particles such as quartz.

Particle lung overload may result in rat lung tumors when air concentrations approach or exceed 2 mg/m³ (Mauderly and McCunney, 1996). The only three animal tests of exposure to crystalline silica which showed a positive carcinogenic effect in the rat lung have all been performed under conditions of particle overload. Lung tumors were observed in rats exposed to quartz at concentrations of 52 mg/m³ (Dagle *et al.*, 1986), 12 mg/m³ (Holland *et al.*, 1986) and 1 mg/m³ (Muhle *et al.*, 1989, 1995). Although Muhle *et al.* (1989) observed increased lung tumor incidence at levels of just below 2 mg/m³, this study also represents an overload condition when the relevant particle size is also taken into consideration (see McClellan, 1996). In addition, the lack of an apparent dose-response over a wide range of exposure concentrations (1-52 mg/m³) is indicative of a non-specific response unique to the rat to foreign particulates having a particular size and surface characteristics, rather than a biologically-specific response that is likely to occur in humans.

The carcinogenic response of the rat to respirable crystalline silica is not predictive for humans because of the rat's enhanced immunological response to crystalline silica. IARC has found that the evidence points to an immunologically-mediated mechanism of carcinogenicity for crystalline silica.

IARC found that this mechanism was sufficiently compelling to explain the basis of the rat's unique response to quartz. Specifically, the rat's sensitive immunological response to inhaled quartz particles initiates a unique species-specific sequence of events leading to tumor formation that is not representative of the human response and is, therefore, inappropriate to extrapolate to humans. Thus, tests of respirable crystalline silica in rats are not predictive of carcinogenicity in humans.

No evidence of direct genotoxicity has been found with any form of crystalline silica. Although Daniel *et al.* (1995) used *in vitro* studies to demonstrate silica binding directly to the backbone of DNA, there is no evidence that this occurs *in vivo*. Based upon the evidence, IARC concluded that there is no convincing evidence that crystalline silica is a direct genotoxin (IARC 1997 Monograph, p. 210).

Without exception, all reported animals studies of crystalline silica (and thus all those reviewed by IARC) used the fractured occluded form of the chemical (IARC 1997 Monograph, pp. 43 and 150-168). As a result, none of the animal data, whether positive or negative, is predictive of the carcinogenicity of unfractured occluded quartz and/or low crystallinity polycrystalline quartz or of quartz from non-occupational sources. Although IARC found sufficient evidence in animals, it did not expand the scope of its overall evaluation of quartz carcinogenicity beyond those occupational sources that were studied. Non-occupational sources of respirable quartz remain unclassified by IARC even when animal data are taken into account. Thus IARC concluded that the positive animal studies it evaluated did not establish a causal relationship relevant to non-occupational exposures to unfractured quartz.

The Background Document presented to the National Toxicology Program (NTP), and prepared by Technology Planning and Management Corporation, in support of the NTP reclassification states that "respirable crystalline silica (RCS) is *known to be a human carcinogen*, based on findings of increased lung cancer rates in occupational groups exposed to crystalline silica dust, and supporting animal and mechanistic data". We believe this characterization of IARC's evaluation of the animal data is incorrect. If IARC had reached the conclusion that animal data was predictive of human response, it would have been compelled by its classification procedures to expand the scope of its classification to nonoccupational sources. IARC did not expand its classification to nonoccupational sources and, instead, limited its findings only to specific biologically active forms of quartz.

concentrations of inert dusts as well. Consequently, *it appears that these studies are not relevant for human risk assessment.*²

2) CRARM. Most recently, the CRARM mirrored the same concerns: "There are . . . cases . . . where rodent tumor responses have been shown to be *irrelevant* to humans" ³ (Emphasis added.) "Some rodent cancer responses [that] should be classified as irrelevant to human cancer risk assessment" include "overwhelming of clearance mechanisms in the rat lung." Table 4-2. The CRARM recommended that if a chemical produces tumors as a result of mechanisms that are not relevant to humans, "that chemical should not be regulated as a carcinogen and should not require extensive risks assessment."⁴

Conclusion statements

Based on the foregoing, The Clorox Company requests that unfractured occluded quartz and low crystallinity polycrystalline quartz be delisted from the Report on Carcinogens. There is no human, animal or other data to support the continued listing of these forms of respirable silica. If you have further questions regarding this submittal, please call Dr. David Crawford at (925)847-6629 or by email at david.crawford@clorox.com.

² (Emphasis added.) CASAC Letter to C.M. Browner, US EPA, August 3, 1995. US EPA's 1996 draft cancer guidelines also note the significance of mechanistic information in evaluating the relevance of tumorigenic response. (61 F.R. 17961, April 23, 1996.).

As early as 1988, US EPA recognized that the rat lung was not a predictor of health effects of inert particulates in human. In 1986, TiO₂ had been listed under SARA § 313 on the basis of positive inhalation studies in rats under overload conditions. US EPA delisted it in 1988 on the ground that the rat response was unique and, therefore, not a sufficient basis for determining carcinogenicity. 53 F.R. 23108, June 20, 1988. See also US EPA's proposed rule to delist TiO₂, 53 F.R. 5006, February 19, 1988. US EPA stated: "In an inhalation bioassay involving multiple dose levels, carcinogenic effects were noted in rats at the high dose level . . . only. The single positive effect appears to have been at a dose level that overwhelmed normal clearance mechanisms in the lung *which leads to a questionable relevance of this finding.*" Interestingly, US EPA delisted even though there was not at that time - as there is for unfractured quartz - reliable epidemiology for TiO₂.

³ CRARM Report, Volume 2, 1997 p. 65. "Grossly overloading the rat lung's clearance mechanisms by administering particles directly to the lung has also been considered irrelevant to humans (Oberdorster, 1995). EPA delisted titanium dioxide from the Toxics Release Inventory in 1988 for this reason (Fed. Reg. 53:23107-23202, 1988). The phenomenon may be applicable to particles in general, not only to titanium dioxide." (CRARM Report, Vol. 2, 1997, p. 67.)

⁴ CRARM Report, Volume 2, 1997, p. 65. and Table 4-2.

National Toxicology Program

NTP has recommended that anomalous responses and use of mechanistic knowledge be considered in hazard identification. The Criteria for Listing Agent, Substances or Mixtures in the Report on Carcinogens states that:

"conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgement, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans". (61 F.R. 50500, September 26, 1996.)

In the case of unfractured occluded quartz or low crystallinity polycrystalline quartz, the data justify a conclusion that these agents act through mechanisms which do not operate in humans.

U.S. Environmental Protection Agency (EPA) and the Presidential Congressional Commission on Risk and Risk Management

The EPA and the Presidential Congressional Commission on Risk Assessment and Risk Management ("CRARM") have concluded that experimental data from rats subjected to conditions of overload by relatively inert particles is not relevant to identification of carcinogenicity in humans. The EPA's Clean Air Act Science Advisory Committee has expressed concern that the cancer-causing mechanism in the rat, related to particle lung overload, may be unique to the rat and does not appear to occur in other species including humans,

1) EPA. The USEPA's Clean Air Act Science Advisory Committee (CASAC) expressed concerns on the use of the response in rats to particulates as basis for hazard identification.

"The cancer-causing mechanism in the rat may be unique to the rat and does not appear to occur in other species including humans. The mechanism in rats is apparently related to particulate overload followed by a sequence of events beginning with inflammation and ending in tumorigenesis. These events are conditioned upon particle overload, which also occurs in rats exposed to high